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StreptomeDB: a resource for natural compounds isolated from *Streptomyces* species

Xavier Lucas, Christian Senger, Anika Erxleben, Björn A. Grüning, Kersten Döring, Johannes Mosch, Stephan Flemming and Stefan Günther*

Pharmaceutical Bioinformatics, Institute of Pharmaceutical Sciences, Albert-Ludwigs-University, D-79104 Freiburg, Germany

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ABSTRACT

Bacteria from the genus *Streptomyces* are very important for the production of natural bioactive compounds such as antibiotic, antitumour or immunosuppressant drugs. Around two-thirds of all known natural antibiotics are produced by these bacteria. An enormous quantity of crucial data related to this genus has been generated and published, but so far no freely available and comprehensive database exists. Here, we present StreptomeDB (http://www.pharmaceutical-bioinformatics.de/streptomedb/). To the best of our knowledge, this is the largest database of natural products isolated from *Streptomyces*. It contains >2400 unique and diverse compounds from >1900 different *Streptomyces* strains and substrains. In addition to names and molecular structures of the compounds, information about source organisms, references, biological role, activities and synthesis routes (e.g. polyketide synthase derived and non-ribosomal peptides derived) is included. Data can be accessed through queries on compound names, chemical structures or organisms. Extraction from the literature was performed through automatic text mining of thousands of articles from PubMed, followed by manual curation. All annotated compound structures can be downloaded from the website and applied for *in silico* screenings for identifying new active molecules with undiscovered properties.

INTRODUCTION

Streptomyces, a well-studied genus of Gram-positive bacteria, belongs to the phylum Actinobacteria. These bacteria present a strikingly similar lifestyle to that of filamentous fungi and, like those, most streptomycetes live as saprophytes in the soil. They also successfully inhabit a wide range of other terrestrial and aquatic niches, and some strains are plant and animal pathogens (1). About 500 different species and thousands of strains and isolates are described in the literature (2,3), accounting for an extremely diverse pool of secondary metabolites produced from several synthesis routes. In fact, almost half of all known natural products (NPs) are produced by 'actinomycetes' (mainly *Streptomyces*) (1,4). Even though these soil-dwelling organisms are better known as antibiotic producers—over two-thirds of the clinically useful antibiotics are isolated from *Streptomyces* (5)—the secondary metabolites have a wide bioactive and therapeutic spectrum. Approved antitumour drugs such as the anthracycline antibiotic daunorubicin or the bleomycin complex, and autoimmune active agents such as the macrolide tacrolimus, among many others, are NPs exclusively produced by *Streptomyces*. Both novel and rare chemical scaffolds with therapeutically relevant activities have been discovered (6–8), like the unprecedented C-5 spirocyclic fusion found in the antitumour fredericamycin A or the unique cyclohexa-1,2,4-triketone moiety of fredericamycin E (9). Genetic manipulation of *Streptomyces* has been used to generate highly diverse chemical libraries by modification of synthesis routes (10–13). Altogether, these facts highlight the renewed interest from academia and the pharmaceutical industry in exploring NP libraries for compounds with novel scaffolds showing therapeutic activity (14).

Here, we present StreptomeDB, a database of compounds isolated from *Streptomyces* spp. The information included was collected from text mining and manual curation of thousands of abstracts and full papers using a newly developed in-house platform and two external databases. StreptomeDB contains data regarding the producing strains, the synthesized compounds, their biological activity and the synthesis route, if available. It also features citations to scientific literature and the chemical

*To whom correspondence should be addressed. Tel: +49 761 2034871; Fax: +49 761 20397769; Email: stefan.guenther@pharmazie.uni-freiburg.de

The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors.

structure and physico-chemical properties of the compounds. To the best of our knowledge, it is the largest compilation of NPs produced by *Streptomyces* spp., including annotations on activities (e.g. antibiotic, antitumour or antifungal) and synthesis routes (e.g. polyketide synthase (PKS)-, non-ribosomal peptide synthase (NRPS)- or terpene-derived compounds). The database can be accessed by producer name, compound name, similarity and substructure chemical queries, biological activity and synthesis route annotation. Furthermore, it features a 'most common substructure selection' (MCSS) panel containing the most frequent occurring substructures within the available chemical space, allowing for the fast and efficient selection of compound families (e.g. β-lactams and tetracyclines).

StreptomeDB brings a unique tool to researchers in both academia and the pharmaceutical industry for the study of secondary metabolites and the discovery of therapeutically relevant novel compounds from natural sources. To facilitate the use of the compounds in *in silico* screenings for the identification of new active molecules, all structures including their annotations can be downloaded from the website as a structure data file. The database is freely accessible at http://www.pharmaceutical-bioinformatics.de/streptomedb.

DATA AND METHODS

Extraction of information in abstracts

All articles available in PubMed were searched for the term 'streptomyces' in medical subject heading (MeSH) terms, keywords, titles and abstracts. For the resulting articles, the abstracts were screened for potential compound names using the CIL database (15), yielding around 15 600 abstracts which potentially contained information on compounds produced by *Streptomyces* spp. A team of seven experts in the field of streptomycetes, their products and the mode of action of antibiotics from biology, chemistry, bioinformatics and pharmaceutical sciences were reading and annotating over 8400 abstracts (including all abstracts of the last 3 years) using full texts if needed with an in-house software module. Texts were searched for the following types of entities: compounds, producing organisms, activities of the compound and the synthesis pathways. The latter were defined as part of or gene cluster for certain pathways specific for the synthesis of secondary metabolites such as antibiotics. This included terpene, shikimate, ribosomal peptide synthetases (RPSs), NRPSs and PKSs pathways.

Identical test sets containing 10 abstracts were used in the beginning to compare and adjust the curation attitude and reliability of the different curators in three rounds with subsequent refinements of entity definitions, resulting in fixed and mandatory guidelines for curation. Unique identifiers were assigned to the terms of the annotated entities. For most compounds, structural descriptions were inherited from the PubChem database if available or drawn. Organism names were unified and organized in a 'main organism' and 'strains/mutant' hierarchy. Activities and synthesis routes were stored with the annotated text parts and additionally classified by keywords.

Curation work yielded around 5700 abstracts and full texts containing information on *Streptomyces* spp. producing one or more compounds and describing compound activities or synthesis routes. All remaining articles contained no such information in the abstracts or available full texts. In 2250 annotated abstracts, compound and organism names did not allow for the assignment of unique identifiers. Thus, they are subject to on-going curation.

Inclusion of data from existing data sources

To complete, enlarge and confirm the body of available information in StreptomeDB, existing data sources with new and overlapping data were used: the thesaurus of the MeSH, the KNApSAcK database (16) and the Novel Antibiotics DataBase (NADB) (http://www0.nih.go.jp/~jun/NADB/search.html), containing substances first reported in the *Journal of Antibiotics* (http://www.antibiotics.or.jp/journal/ja-top.htm). Descriptions of MeSH were queried for compounds with descriptions specifying an organism which could be uniquely identified. In MeSH descriptions, 83 compound–organism relationships could be found and unique identifiers for compounds and organisms were assigned. Data from the NADB are available through its 'Namazu: a full text search engine' interface (http://www0.nih.go.jp/~jun/NADB/namazu.cgi?query=streptomyces, accessed 25 July 2012). It provided 2557 abstracts of which 1225 unique identifiers could be assigned to compounds and organisms. The KNApSAcK database contains 1988 metabolite–*Streptomyces* spp. relationships with one or more associated literature references (http://kanaya.naist.jp/knapsack_jsp/result.jsp?sname=organism&word=streptomyces, accessed 25 July 2012). For 1245 of those compound–organism references, unique identifiers for compounds and organisms could be assigned.

Failure of assignment of unique identifiers

Failure of assignment of unique identifiers to compound and organism names in the three existing data sources and the curated abstracts was caused by ambiguous names, spelling and curation errors which could not be traced back, or compound names and synonyms which were not available in PubChem or any other freely accessible database.

Searching with most common substructures

To enable the user to search with common substructures, all compounds were fragmented using the RECAP algorithm (17). The 120 most frequent fragments containing a cyclic structure occurring as substructures in all StreptomeDB compounds are presented to the user for selection.

Data were stored in a PostgreSQL database (PostgreSQL 8.4.8, PostgreSQL Global Development Group). All calculations of chemical properties were executed using Open Babel 2.3.0 (18).

RESULTS

Compound diversity

The database contains >2400 different secondary metabolites produced by *Streptomyces* spp. (Table 1). Diverse compound classes such as anthracyclines and cyclic peptides are included (Figure 1). The large proportion of very complex compounds results in a much higher average molecular weight (median: 453 g/mol) compared with typical drugs (median: 310 g/mol, 19). For example, the approved antibiotic drug actinomycin has a molecular weight of 1255 g/mol.

The MCSS panel for compound selection (Figure 2) is based on substructures that can be synthetically combined and are common in drug-like molecules. The panel highlights the large diversity of the rings present in the NPs of StreptomeDB (Figure 1). For example, 60 β-lactam antibiotics and 50 antitumour anthracyclines are included in the database (20). The MCSS panel allows a direct selection and identification of compounds containing such substructures.

Activities and synthesis routes

Many pharmaceutically relevant peptides are synthesized by NRPSs (21). Such compounds are characterized by an extremely broad range of biological activities, pharmacological properties and rare structural features. NRPS-derived compounds annotated in StreptomeDB include cytostatic agents such as epothilone or bleomycin, or antibiotics such as daptomycin or enduracidin. For other compounds of that class, the broad range of activities has not been clarified yet and remains subject to further research (22).

The 217 compounds annotated as PKSs derived are the largest group of StreptomeDB. Analogous to NRPS-derived compounds, they are an important source for pharmacologically relevant molecules (23). Many of the therapeutically used antibiotics, such as tetracyclines are produced by PKS. Examples of important polyketides included in StreptomeDB with annotated activity are the antibacterial oxytetracycline and the anticancer geldanamycin (24). Additional synthesis routes include terpene synthesis or RPS.

For 875 NPs, activity information is included in the database. The annotations contain very specific descriptions (e.g. inhibitor of protein X) as well as more unspecific classifications (e.g. antibiotic). In total, 71 different activity classifications have been included in the database.

Case studies

The database enables fast delivery of information related to research in pharmaceutical sciences or chemistry. Some examples for possible applications are explained in the following.

Drug discovery

Many NPs have therapeutically relevant activities (25). To start a general search for bioactive compounds, it is useful to have a deeper look on substructures known to be active and which appear in several drugs (26). For example, phenazine compounds possess activities on several target proteins because of their ability to promote electron transfer (27). Particularly, the effect on G-protein-coupled receptors (GPCRs) is demonstrated by several phenazine-containing drugs (28).

StreptomeDB contains 26 phenazines. Structures can be easily selected through the MCSS panel (Figure 2). Assaying the activities of NPs on GPCRs or other known drug targets may reveal some new specific therapeutic functions. Recently, Ohlendorf *et al.* (29) could show that the phenazine geranylphenazinediol extracted from a marine *Streptomyces* spp. is a potent inhibitor of the human acetyl-cholinesterase.

Search for enzymes able to catalyse specific synthesis steps

Aziridine-containing NPs are extremely rare (30). However, the DNA alkylating and crosslinking activities of aziridine analogues have been shown to be attractive for the development of anti-leukaemia therapeutics (31). The knowledge about the organisms, gene clusters and enzymes that can synthesize such ring systems may enable the design of chemotherapeutic agents with enhanced stability and tumour selectivity which can be produced by genetically modified enzymes (30).

A substructure search in StreptomeDB starting with aziridine results in 13 compounds containing this functional group (Figure 3). The related links lead to the producing organisms and to the source publications. Specifically, Zhao *et al.* (32) describe a PKS-gene cluster which is involved in the pathway for the synthesis of azinomycin B. This is a very good starting point for the identification of associated genes and the investigation of the enzymatic mechanism responsible for building important groups such as aziridine rings.

Search for antibiotics effective against newly resistant bacteria

Overtreatment with antibiotics has led to bacterial strains resistant against several known antibiotics (33). Yet, no longer used antibiotics have been successfully administered in the treatment of therapeutic infections caused by resistant bacteria (34).

In StreptomeDB, many antibiotics are described which were never or rarely used as clinical drugs. An activity

Table 1. Content of StreptomeDB (accessed 9 October 2012)

Compounds (No.)	2444	Annotated PKS-synthesized compounds (No.)	256
Molecular weight [g/mol] (median)	452.5	Annotated NRPS-synthesized compounds (No.)	51
Compounds that fit to the Lipinski's Rule of Five (No.)	1522	Different organisms, including strains (No.)	1985
Compounds annotated with activity (No.)	1036	Referenced articles (No.)	4544
Compounds annotated with structure (No.)	2444	Number of compound–organism relationships (No.)	4341

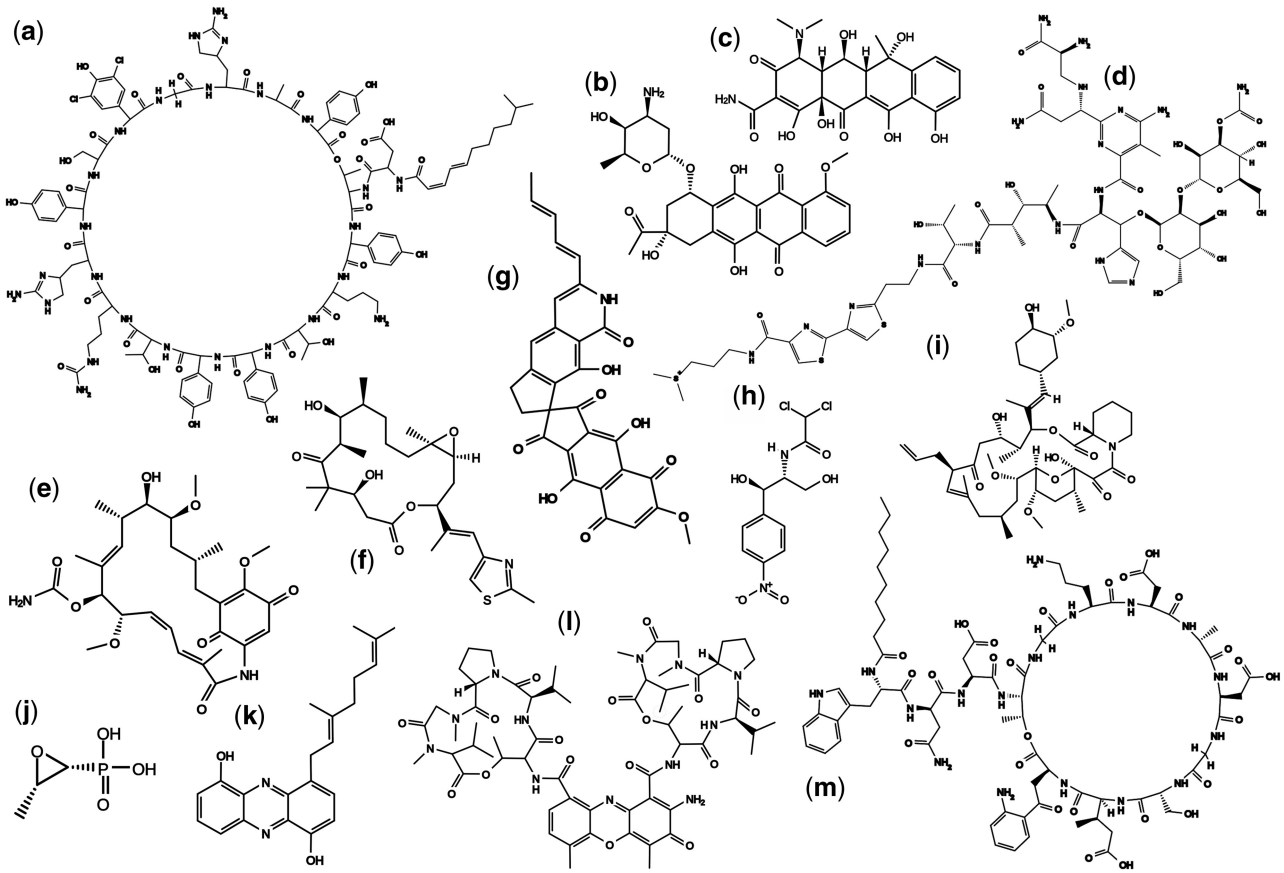

Figure 1. Examples of NPs produced by *Streptomyces* spp. included in StreptomeDB. (**a**) Enduracidin A, NRPS-derived antibiotic; (**b**) daunorubicin, antitumour anthracycline; (**c**) oxytetracycline, tetracycline antibiotic; (**d**) bleomycin, NRPS/PKS-derived anticancer; (**e**) geldanamycin, macro-cyclic Hsp90 inhibitor; (**f**) epothilone B, anticancer macro-cycle; (**g**) fredericamycin A, C-5 spirocyclic DNA-polymerase inhibitor; (**h**) chloramphenicol, broad-spectrum antibiotic; (**i**) tacrolimus, macro-cyclic immunosuppressive; (**j**) fosfomycin, broad-spectrum antibiotic; (**k**) geranylphenazinediol, acetyl-CoA inhibitor; (**l**) actinomycin, NRPS/PKS-derived antineoplastic agent and (**m**) daptomycin, NRPS-derived antibiotic.

search in the database starting with 'antibiotic' results in a list of described antibiotics with the related publications. Antibiotics described long ago such as fosfomycin or chloramphenicol may be still active against highly resistant strains when administered either on their own or in combination with other antibiotics (35,36).

DISCUSSION AND FUTURE PROSPECTS

Different statements exist about the total number of NPs which are synthesized by *Streptomyces* spp. Some years ago, Bérdy (4) reported a number of 3000 bioactivities but the referenced source database is no longer available and it remains unclear which compounds are meant. KNApSAcK and NADB databases list ~1500 compounds which are synthesized by *Streptomyces*. StreptomeDB has currently annotated around 2400 unique compounds but the number is continuously increasing. One reason for not including all compounds that are described is that important information is included in the full texts but is not necessarily in the abstracts of articles. The detailed analysis of related full texts is subject to an on-going project which will further increase the dataset not only for compounds but also for activity data and synthesis routes. Newly published articles are curated and included to the database on a three-monthly basis.

Furthermore, several hundreds of compounds annotated in StreptomeDB were not included in the PubChem database and therefore could not be assigned easily with structures. Since we have started to draw many of those compounds manually, the assignment of all of them with chemical structures is intended.

The interest of researchers in genomic data encoding for synthesizing enzymes of NPs is of growing interest. Knowledge about the enzymatic mechanisms of important synthesis steps enables the production of chemicals which can be produced in engineered organisms (10–13). Databases describing genes and gene clusters encoding for important enzymes involved in pathways for the production of NPs exist [e.g. NORINE (22) and NRPS-PKS (37)] but a lot of important data are still hidden in publications as text information. StreptomeDB complements existing datasets and supports data collection projects dealing with biological chemistry by allowing recognition of organisms containing enzymes which are able to catalyse important functional groups and specific synthesis steps. More detailed information about involved pathways and related genes responsible for compound

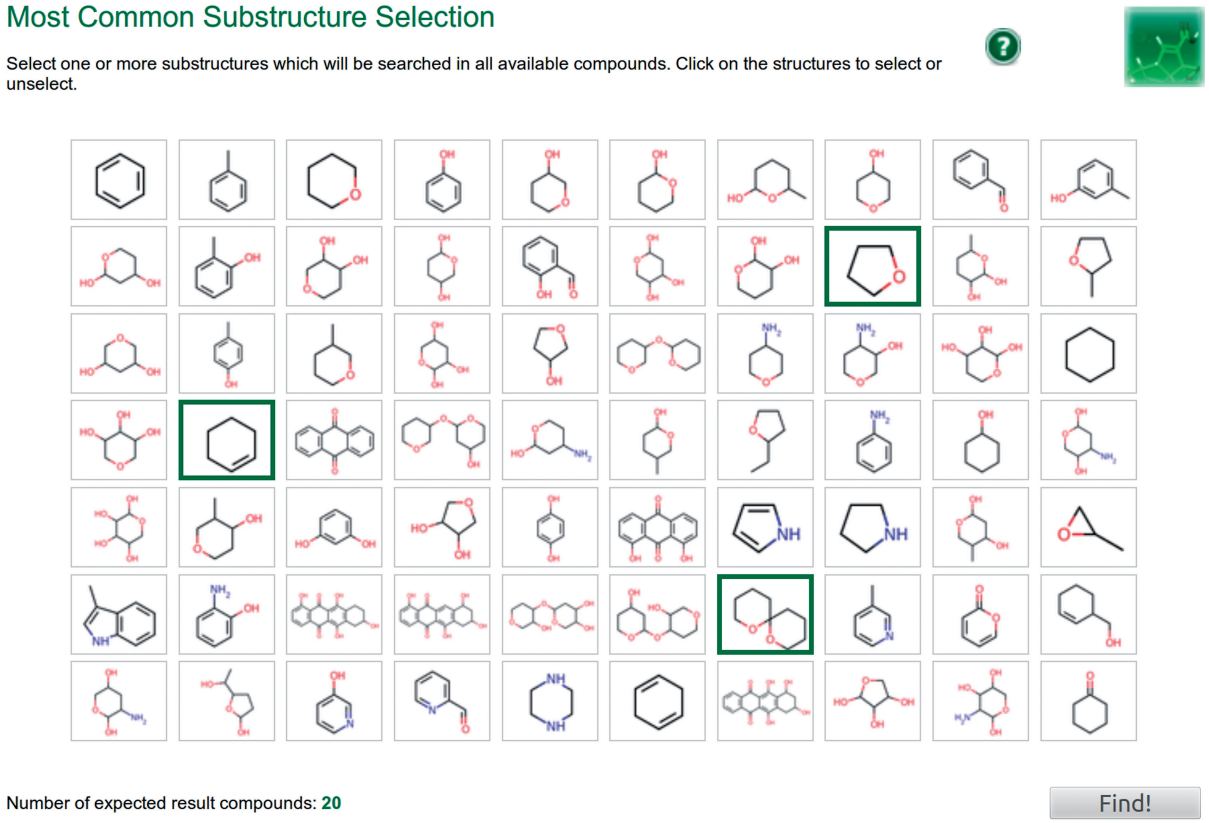

Figure 2. MCSS panel in StreptomeDB, featuring the most common cyclic structures included in the database.

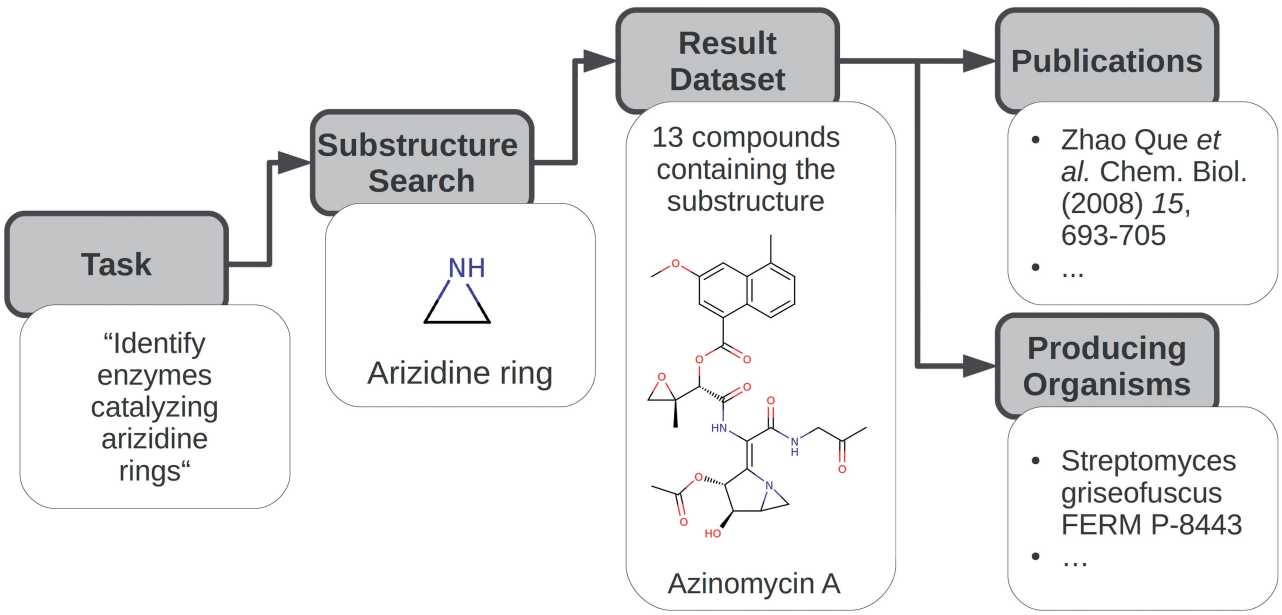

Figure 3. Workflow of a substructure search for arizidine-containing compounds in StreptomeDB.

synthesis would be of interest for the research community. Even though most of this information is not yet described in the literature, the inclusion of the available data will be part of StreptomeDB in future updates.

We provide the complete dataset for download including the structural information. This opens the possibility for modelling molecular interactions on the structural level. *In silico* screening approaches for the

identification of new drugs are becoming more and more important (38–40). We believe that the presented dataset is a valuable molecular library for the virtual screening of therapeutically important target proteins. For many NPs, the complete activity spectrum is not clarified yet. The supplied data will help identifying NPs or analogues useful as candidates of new active compounds.

CONCLUSION

To the best of our knowledge, StreptomeDB is the largest database describing NPs produced by streptomycetes. Downloadable chemical structures allow for the application in virtual screening. Collected data will support analyses of gene clusters and associated enzymes responsible for the synthesis of functional groups. *Streptomyces* is the most important genus for the production of therapeutic NPs. Thus, the database will be of interest for researchers working in the area of drug discovery and chemistry.

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